Claim 1 herein is amended by deleting the offending language "susceptible to or diagnosed" to address the clarity rejection raised by the Examiner (see below). In addition, the language "an effective amount of" has been deleted and the phrase "in an amount effective to treat the disorder" has been added to the end of the claim to address the further clarity rejection raised by the Examiner (see below). Support for this language is found throughout the specification, but especially on pages 15 and 38-41. The "gemcitabine" chemotherapeutic agent disclosed on page 17, line 15 has been inserted into claim 1 (and thus dependent claim 12) to address various 102/103 rejections (see below). Hence the cancellation of claims 10 and 11 as moot.

Claims 7 and 17 have been amended to address the Examiner's clarity rejection in the first two lines of page 4 of the Office Action.

Claim 14 includes the language "and further indicating that said composition can be combined with gemcitabine" to address the double patenting rejections in items 1-3 on page 2 of the Office Action. Support for this language is found on page 17, line 15, for instance.

Claims 15 and 16 have been amended for claim precision to state that the further instructions are found on the package insert.

Responsive to the clarity rejection, claims 20 and 32 refer to a "cardioprotectant which prevents or reduces myocardial dysfunction" as supported on page 20, lines 8-9 of the application for instance.

The Markush group listings in claims 22 and 24 have been amended for claim precision in accordance with the Examiner's suggestions on page 4 of the Office Action.

Finally, the offending language in claim 27 has been removed to address the Examiner's clarity rejection with respect to this claim.

In that the amendments do not introduce new matter, their entry is

respectfully requested.

Double Patenting

Claims 1-19 are said to conflict with claims 1-19 of USSN 09/208,649 (hereinafter "the '649 application"). This objection is moot in view of the amendment of the claims in the '649 application and in the present application.

Claims 1-19 are provisionally rejected under 35 USC Section 101 as claiming the same invention as that of claims 1-19 of the '649 application. This objection is moot in view of the amendment of the claims in the '649 application and in the present application.

112, 2nd paragraph

Claims 1-31 are rejected under 35 USC Section 112, second paragraph, as allegedly being indefinite. The various bases of this rejection will be addressed individually below.

Claims 1-19 are considered to be unclear in the recitation "susceptible to a disorder characterized by overexpression of ErbB2 receptor" or "a condition characterized by". In the interests of expediting prosecution, the language "susceptible to or diagnosed" is hereby removed from claim 1 as moot given the definition of treatment on page 15, lines 9-11 of the application. As to the language "a condition characterized by overexpression of ErbB2 receptor", Applicants submit that ErbB2 overexpression is an art-recognized term, and can be readily assessed, *e.g.* by immunohistochemistry or FISH (see page 44, lines 1-7 of the application for instance).

Claims 1-13 and 20-31 are thought to be unclear with respect to the recitation of an "effective amount" or "efficacy". Without agreeing with the appropriateness of the rejection and, in order to expedite prosecution, claim 1 is amended herein to recite that the amount of the combination administered to the human patient is effective to treat the disorder. As to claim 20 and its dependent claims, Applicants traverse

this rejection. Applicants submit that it would be abundantly clear to the skilled physician from reading the present application that the amount of the anti-ErbB2 antibody administered should treat the cancer (see, *e.g.* pages 38-41 of the application) and the effective amount of the cardioprotectant is that which reduces or prevents myocardial dysfunction resulting from administration of the anti-ErbB2 antibody (and optionally an anthracycline antibiotic or other chemotherapeutic agent) to the patient. See, for instance, pages 40-41 of the application. To recite all this language in claim 20 would make it less clear because of such excessive language therein.

Claims 15 and 16 are considered to be unclear in the recitation of a label on or associated with the container. The rejection is moot in view of the amendment of claims 15 and 16 to refer to the package insert.

Claim 17 is considered to be unclear with respect to the recitation "the receptor". This rejection is overcome by the amendment of the claim to refer to binding to "an extracellular domain of ErbB2 receptor". Likewise, the amendment of claim 7.

Claims 20-29 and 30-33 are considered to be unclear with respect to the recitation of a "cardioprotectant". This is addressed herein by inclusion of the language "which prevents or reduces myocardial dysfunction" in claims 20 and 32.

Claims 22 and 24 are thought to be unclear because of improper Markush groups. This is addressed by inclusion of the missing "and" in claim 22 and amendment of claim 24 as suggested by the Examiner.

Finally, claim 27 is thought to be unclear in the recitation of "administered with". Hence the removal of the offending language from the claim.

Reconsideration and withdrawal of the clarity rejections is respectfully requested in view of the above.

Section 102

Claims 1-13 are rejected under 35 USC Section 102(a) as being anticipated by Baselga *et al. Oncology* 11(3) Suppl 2:43-47 (1997) (hereinafter "Baselga I").

This novelty rejection is moot in view of the amendment of claim 1 herein to recite administering a combination of an anti-ErbB2 antibody and gemcitabine to the human patient, which is not disclosed in Baselga I. Reconsideration and withdrawal of the novelty rejection based on Baselga I is respectfully requested in view of the amendment of claim 1 herein.

Claims 1-11 are rejected under 35 USC Section 102(a) as being anticipated by Norton, *Seminars in Oncology* 24(4), Suppl 10:S10-3 - S10-10 (August, 1997) (hereinafter "Norton").

This novelty rejection is moot in view of the amendment of claim 1 herein to recite administering a combination of an anti-ErbB2 antibody and gemcitabine to the human patient, which is not disclosed in Norton. Reconsideration and withdrawal of the novelty rejection based on Norton is respectfully requested in view of the amendment of claim 1 herein.

Claims 1-5, 7-9 and 12 are rejected under 35 USC Section 102(b) as being anticipated by Lippman *et al.* US Patent No. 5,578,482 (hereinafter "the '482 patent") or Hynes *et al. Biochimica et Biophysica Acta* 1198:165-184 (1994) (hereinafter Hynes *et al.*). Claims 1-5 and 12 are rejected under 35 USC 102 as being anticipated by Arakawa *et al.* US Patent No. 5,783,186 (hereinafter "the '186 patent").

These novelty rejections are moot in view of the amendment of claim 1 herein to recite administering a combination of an anti-ErbB2 antibody and gemcitabine to the human patient, which is not disclosed in the '482 or '186 patents, or in Hynes *et al.* Reconsideration and withdrawal of the novelty rejections based on these three citations is respectfully requested in view of the amendment of claim 1 herein.

Section 103

Claims 1-9 are rejected under 35 USC Section 103(a) as being unpatentable over Hudziak *et al.* US Patent No. 5,770,195 (hereinafter "the '197 patent").

This rejection is moot in view of the recitation of "gemcitabine" in claim 1. Reconsideration and withdrawal of the rejection based on the '197 patent is respectfully requested in view of the above.

Claims 1-13 are rejected under 35 USC Section 103 as being unpatentable over Baselga *et al. J. Clin. Oncol.* 14(3) 737-744 (1996) (hereinafter "Baselga II") in view of Hynes *et al.*

Applicants submit that the method set forth in claims 1-13 as amended herein would not have been obvious in view of Baselga II and Hynes *et al.* Claim 1 as amended herein recites administration of a combination of an anti-ErbB2 antibody and gemcitabine to the human patient. This selection invention was not disclosed or suggested by Baselga II and Hynes *et al.* Thus, Applicants submit that the invention set forth in claims 1-13 would have been nonobvious over the cited references. Reconsideration and withdrawal of the Section 103 rejection is respectfully requested.

Claims 1-33 are rejected under 35 USC 103(a) as being unpatentable over Baselga II or Norton in view of Singal *et al. J. Molec. Cell Cardiol.* 27: 1055-1063 (1995) (hereinafter "Singal *et al.*") and further in view of Seifert *et al. Annals Pharmacotherapy* 28: 1063-1072 (1994) (hereinafter "Seifert *et al.*"). Claims 1-5, 7-9, 12 and 14-33 are rejected as being unpatentable over the '482 patent in view of Singal *et al.* and further in view of Seifert *et al.* Claims 1-5, 7-9, 12 and 14-33 are rejected under 35 USC Section 103 as being unpatentable over Hynes *et al.* in view of Singal *et al.* and further in view of Seifert *et al.* Claims 1-5, 12 and 14-33 are rejected under 35 USC Section 102(a) as being unpatentable over the '186 patent in view of Singal *et al.* and further in view of Seifert *et al.*

Applicants submit that the presently claimed invention would not have been obvious from the cited references at the time of filing.

As noted above, the cited references fail to teach combining an anti-ErbB2 antibody and gemcitabine, and hence Applicants submit that claims 1 and 14 and the claims which depend thereon are clearly patentable over the cited art.

Aside from the selection invention of combining an anti-ErbB2 antibody and gemcitabine, there is nothing in the cited references to indicate that one should avoid the use of anthracycline-type chemotherapeutics in combination with an anti-ErbB2 antibody, or administer a cardioprotectant to a patient treated with an anti-ErbB2 antibody. The present application demonstrates the unexpected result that combining an anthracycline with an anti-ErbB2 antibody may increase the incidence of myocardial dysfunction compared to anthracycline alone (See lines 20-22 on page 47). Thus, the application describes and claims: (1) a method of therapy which avoids combining therapy with an anti-ErbB2 antibody and an anthracycline derivative; (2) a package insert with a warning to avoid such combined therapy; (3) a method involving administering a cardioprotectant to anti-ErbB2-treated patients; and (4) an article of manufacture which instructs a user to treat a patient with an anti-ErbB2 antibody and a cardioprotectant. Accordingly, Applicants submit that the claims are clearly patentable over the cited documents.

In order to expedite prosecution, the undersigned specifically requests the opportunity to discuss this case with the Examiner in either a personal or telephone interview following entry of this amendment. The Examiner is invited to call the undersigned at the number noted below concerning this.

Respectfully submitted,
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